16th Edition

HARRISON'S PRINCIPLES OF Internal Medicine

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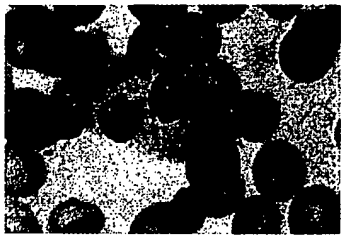

FIGURE 55-5 Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration.

nitric oxide also participate in microbial killing. Other enzymes, such as lysozyme and acid proteases, help digest microbial debris. After 1 to 4 days in tissues neutrophils die. The apoptosis of neutrophils is also cytokine-regulated; granulocyte colony-stimulating factor (G-CSF) and IFN-γ prevent their death. Under certain conditions, such as in delayed-type hypersensitivity, monocyte accumulation occurs within 6 to 12 h of initiation of inflammation. Neutrophils, monocytes, microorganisms in various states of digestion, and altered local tissue cells make up the inflammatory exudate, pus. Myeloperoxidase confers the characteristic green color to pus and may participate in turning off the inflammatory process by inactivating chemoattractants and immobilizing phagocytic cells.

Neutrophils respond to certain cytokines [IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8] and produce cytokines and chemotactic signals [TNF-α, IL-8, macrophage inflammatory protein (MIP) 1] that modulate the inflammatory response. In the presence of fibrinogen, f-metleuphe or leukotriene B_4 induces IL-8 production by neutrophils, providing autocrine amplification of inflammation. *Chemokines* (chemoattractant cytokines) are small proteins produced by many different cell types, including endothelial cells, fibroblasts, epithelial cells, neutrophils, and monocytes, that regulate neutrophil and monocyte recruitment and activation. The chemokines transduce their signals through heterotrimeric G protein–linked receptors that have seven cell membrane–spanning domains, the same type of cell-surface receptor that mediates the response to the classic chemoattractants f-metleuphe and C5a. Four major groups of chemokines are recognized based on the cysteine structure near the N terminus: C, CC, CXC, and CXXXC. The CXC cytokines such as IL-8 mainly attract neutrophils; CC chemokines such as MIP-1 attract lymphocytes, monocytes, eosinophils, and basophils; the C chemokine lymphotactin is T cell tropic; the CXXXC chemokine fractalkine attracts neutrophils, monocytes, and T cells. These molecules and their receptors not only regulate the trafficking and activation of inflammatory cells, but chemokine receptors serve as co-receptors for HIV infection (Chap. 173) and have a role in atherogenesis.

NEUTROPHIL ABNORMALITIES A defect in the neutrophil life cycle can lead to dysfunction and compromised host defenses. Inflammation is often depressed, and the clinical result is often recurrent and severe bacterial and fungal infections. Aphthous ulcers of mucous membranes (gray ulcers without pus) and gingivitis and periodontal disease suggest a phagocytic cell disorder. Patients with congenital phagocyte defects can have infections within the first few days of life. Skin, ear, upper and lower respiratory tract, and bone infections are common. Sepsis and meningitis are rare. In some disorders the frequency of infection is variable, and patients can go for months or even years without major infection. Aggressive management of these congenital diseases has extended the life span of patients well beyond 30 years.

FIGURE 55-6 Normal eosinophil and basophil. The eosinophil contains large, bright orange granules and usually a bilobed nucleus. The basophil contains large purple-black granules that fill the cell and obscure the nucleus.

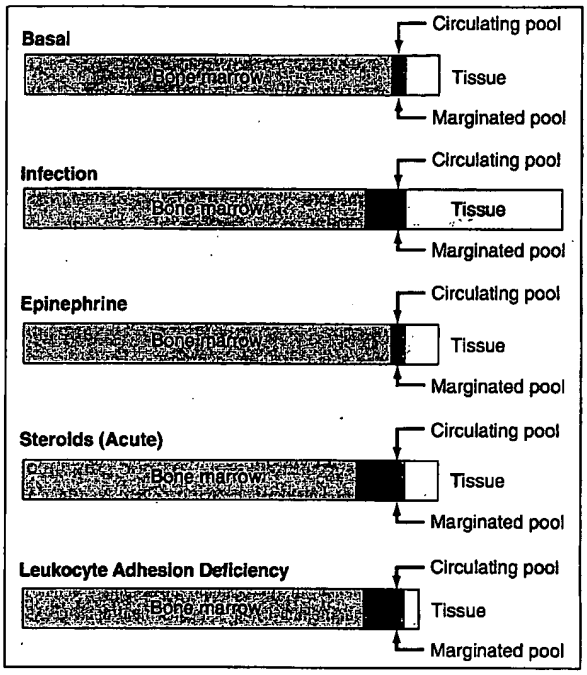

FIGURE 55-7 Schematic neutrophil distribution and kinetics between the different anatomic and functional pools.

Neutropenia The consequences of absent neutrophils are dramatic. Susceptibility to infectious diseases increases sharply when neutrophil counts fall below 1000 cells/μL. When the absolute neutrophil count (ANC; band forms and mature neutrophils combined) falls to <500 cells/μL, control of endogenous microbial flora (e.g., mouth, gut) is impaired; when the ANC is <200/μL, the inflammatory process is absent. Neutropenia can be due to depressed production, increased peripheral destruction, or excessive peripheral pooling. A falling neutrophil count or a significant decrease in the number of neutrophils below steady-state levels, together with a failure to increase neutrophil counts in the setting of infection or other challenge, requires investigation. Acute neutropenia, such as that caused by cancer chemotherapy, is more likely to be associated with increased risk of infection than neutropenia of long duration (months to years) that reverses in response to infection or carefully controlled administration of endotoxin (see "Laboratory Diagnosis," below).

Some causes of inherited and acquired neutropenia are listed in Table 55-1. The most common neutropenias are iatrogenic, resulting from the use of cytotoxic or immunosuppressive therapies for malignancy or control of autoimmune disorders. These drugs cause neutropenia because they result in decreased production of rapidly growing progenitor (stem) cells of the marrow. Certain antibiotics such as chloramphenicol, trimethoprim-sulfamethoxazole, flucytosine, vidarabine, and the antiretroviral drug zidovudine may cause neutropenia by inhibiting proliferation of myeloid precursors. The marrow suppression is generally dose-related and dependent on continued administration of the drug. Recombinant human G-CSF usually reverses this form of neutropenia.

Another important mechanism for iatrogenic neutropenia is the effect of drugs that serve as immune haptens and sensitize neutrophils or neutrophil precursors to immune-mediated peripheral destruction. This form of drug-induced neutropenia can be seen within 7 days of exposure to the drug; with previous drug exposure, resulting in preexisting antibodies, neutropenia may occur a few hours after administration of the drug. Although any drug can cause this form of neutropenia, the most frequent causes are commonly used antibiotics, such as sulfa-containing compounds, penicillins, and cephalosporins. Fever and eosinophilia may also be associated with drug reactions, but

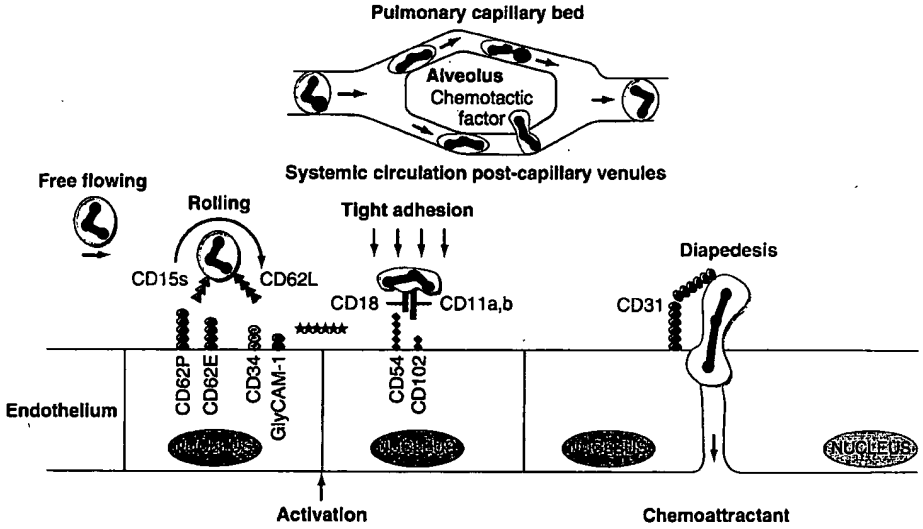

FIGURE 55-8 Neutrophil travel through the pulmonary capillaries is dependent on neutrophil deformability. Neutrophil rigidity (e.g., caused by C5a) enhances pulmonary trapping and response to pulmonary pathogens in a way that is not so dependent upon cell-surface receptors. Intraalveolar chemotactic factors, such as those caused by certain bacteria (e.g., *Streptococcus pneumoniae*) lead to diapedesis of neutrophils from the pulmonary capillaries into the alveolar space. Neutrophil interaction with the endothelium of the systemic postcapillary venules is dependent on molecules of attachment. The neutrophil "rolls" along the endothelium using selectins: neutrophil CD15s (sialyl-Lewis^x) binds to CD62E (E-selectin) and CD62P (P-selectin) on endothelial cells; CD62L (L-selectin) on neutrophils binds to CD34 and other molecules (e.g., GlyCAM-1) expressed on endothelium. Chemokines or other activation factors stimulate integrin-mediated "tight adhesion": CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1, CR3) bind to CD54 (ICAM-1) and CD102(ICAM-2) on the endothelium. Diapedesis occurs between endothelial cells: CD31 (PECAM-1) expressed by the emigrating neutrophil interacts with CD31 expressed at the endothelial cell-cell junction.

often these signs are not present. Drug-induced neutropenia can be severe, but discontinuation of the sensitizing drug is sufficient for recovery, which is usually seen within 5 to 7 days and is complete by 10 days. Readministration of the sensitizing drug should be avoided, since abrupt neutropenia will often result. For this reason, diagnostic challenge should be avoided.

Autoimmune neutropenias caused by circulating antineutrophil antibodies are another form of acquired neutropenia that results in increased destruction of neutrophils. Acquired neutropenia may also be seen with viral infections, including infection with HIV. Acquired neutropenia may be cyclic in nature, occurring at intervals of several weeks. Acquired cyclic or stable neutropenia may be associated with an expansion of large granular lymphocytes (LGL), which may be T cells, NK cells, or NK-like cells. Patients with LGL lymphocytosis may have moderate blood and bone marrow lymphocytosis, neutropenia, polyclonal hypergammaglobulinemia, splenomegaly, rheumatoid arthritis, and absence of lymphadenopathy. Such patients may have a chronic and relatively stable course. Recurrent bacterial infections are frequent. Benign and malignant forms of this syndrome occur. In some patients, a spontaneous regression has occurred even after 11 years, suggesting an immunoregulatory defect as the basis for at least one form of the disorder. Glucocorticoids, cyclosporine, IFN-α, and nucleosides such as 2-chlorodeoxyadenosine each have induced remission.

Hereditary Neutropenias Hereditary neutropenias are rare and may manifest in early childhood as a profound constant neutropenia or agranulocytosis. Congenital forms of neutropenia include Kostmann's syndrome (neutrophil count $< 100/\mu L$), which is often fatal; more benign severe chronic neutropenia (neutrophil count of 300 to 1500/μL) due to mutations in neutrophil elastase; the cartilage-hair hypoplasia syndrome due to mutations in the mitochondrial RNA-processing endoribonuclease, RMRP; Shwachman-Diamond syndrome associated with pancreatic insufficiency due to mutations in the Shwachman-Bodian-Diamond syndrome gene, *SBDS*; myelokathexis, a congenital disorder characterized by neutrophil degeneration, hypersegmentation, and myeloid hyperplasia in the marrow associated with decreased expression of bcl-X_L in myeloid precursors and accelerated apoptosis due to mutations in the chemokine receptor CXCR4; and neutropenias associated with other immune defects (X-linked agammaglobulinemia, ataxia telangiectasia, IgA deficiency). Mutations in the G-CSF receptor on chromosome 1 associated with poor response to G-CSF can develop in severe congenital neutropenia and are linked to myeloid malignancy. Hereditary cyclic neutropenia, an autosomal dominant trait, is typically diagnosed in infancy and is characterized by a remarkably regular 3-week cycle. Hereditary cyclic neutropenia actually is cyclic hematopoiesis, also due to mutations in the neutrophil elastase gene. Glucocorticoids and G-CSF blunt the cycling in some patients.

Maternal factors can be associated with neutropenia in the newborn. Transplacental transfer of IgG directed against antigens on fetal neutrophils can result in peripheral destruction. Drugs (e.g., thiazides) ingested during pregnancy can cause neutropenia in the newborn by either depressed production or peripheral destruction.

The presence of immunoglobulin directed toward neutrophils is seen in Felty's syndrome—a triad of rheumatoid arthritis, splenomegaly, and neutropenia (Chap. 301). Patients with Felty's syndrome who respond to splenectomy with an increase in their neutrophil count also have lower postoperative serum neutrophil-binding IgG. Some of these patients have neutropenia associated with an increased number of LGL. Splenomegaly with peripheral trapping and destruction of neutrophils is also seen in lysosomal storage diseases and in portal hypertension.

Neutrophilia Neutrophilia results from increased neutrophil production, increased marrow release, or defective margination (Table 55-2). The most important acute cause of neutrophilia is infection. Neutrophilia from acute infection represents both increased production and increased marrow release. Increased production is also associated with chronic inflammation and certain myeloproliferative diseases. In-

TABLE 55-1 Causes of Neutropenia

Decreased Production
Drug-induced—alkylating agents (nitrogen mustard, busulfan, chlorambucil, cyclophosphamide); antimetabolites (methotrexate, 6-mercaptopurine, 5-flucytosine); noncytotoxic agents [antibiotics (chloramphenicol, penicillins, sulfonamides), phenothiazines, tranquilizers (meprobamate), anticonvulsants (carbamazepine), antipsychotics (clozapine), certain diuretics, anti-inflammatory agents, antithyroid drugs, many others]
Hematologic diseases—idiopathic, cyclic neutropenia, Chédiak-Higashi syndrome, aplastic anemia, infantile genetic disorders (see text)
Tumor invasion, myelofibrosis
Nutritional deficiency—vitamin B_{12}, folate (especially alcoholics)
Infection—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS
Peripheral Destruction
Antineutrophil antibodies and/or splenic or lung trapping
Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus
Drugs as haptens—aminopyrine, α-methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines
Wegener's granulomatosis
Peripheral Pooling (Transient Neutropenia)
Overwhelming bacterial infection (acute endotoxemia)
Hemodialysis
Cardiopulmonary bypass

TABLE 55-2 *Causes of Neutrophilia*

Increased Production
Idiopathic
Drug-induced—glucocorticoids
Infection—bacterial, fungal, sometimes viral
Inflammation—thermal injury, tissue necrosis, myocardial and pulmonary infarction, hypersensitivity states, collagen vascular diseases
Myeloproliferative diseases—myelocytic leukemia, myeloid metaplasia, polycythemia vera
Increased Marrow Release
Glucocorticoids
Acute infection (endotoxin)
Inflammation—thermal injury
Decreased or Defective Margination
Drugs—epinephrine, glucocorticoids, nonsteroidal anti-inflammatory agents
Stress, excitement, vigorous exercise
Leukocyte adhesion deficiency type 1 (integrin β chain, CD18)
Leukocyte adhesion deficiency type 2 (selectin ligand, CD15s, sialyl-Le^x)
Miscellaneous
Metabolic disorders—ketoacidosis, acute renal failure, eclampsia, acute poisoning
Drugs—lithium
Other—metastatic carcinoma, acute hemorrhage or hemolysis

creased marrow release and mobilization of the marginated leukocyte pool are induced by glucocorticoids. Release of epinephrine, as with vigorous exercise, excitement, or stress, will demarginate neutrophils in the spleen and lungs and double the neutrophil count in minutes. Leukocytosis with cell counts of 10,000 to 25,000/μL occurs in response to infection and other forms of acute inflammation and results from both release of the marginated pool and mobilization of marrow reserves. Persistent neutrophilia with cell counts of ≥30,000 to 50,000/μL is called a *leukemoid reaction*, a term often used to distinguish this degree of neutrophilia from leukemia. In a leukemoid reaction, the circulating neutrophils are usually mature and not clonally derived.

Abnormal Neutrophil Function Inherited and acquired abnormalities of phagocyte function are listed in Table 55-3. The resulting diseases are best considered in terms of the functional defects of adherence, chemotaxis, and microbicidal activity. The distinguishing features of the important inherited disorders of phagocyte function are shown in Table 55-4.

DISORDERS OF ADHESION Two types of leukocyte adhesion deficiency (LAD) have been described. Both are autosomal recessive traits and result in the inability of neutrophils to exit the circulation to sites of infection, leading to leukocytosis and increased susceptibility to infection (Fig. 55-8). Patients with LAD 1 have mutations in CD18, the common component of the integrins LFA-1, Mac-1, and p150,95, leading to a defect in tight adhesion between neutrophils and the endothelium. The heterodimer formed by CD18/CD11b (Mac-1) is also the receptor for the complement-derived opsonin C3bi (CR3). The CD18 gene is located on distal chromosome 21q. Variable expression of the defect determines the severity of clinical disease. Complete lack of expression of the leukocyte integrins results in severe phenotype in which inflammatory stimuli do not increase the expression of leukocyte integrins on neutrophils or activated T and B cells. Neutrophils (and monocytes) from patients with LAD 1 adhere poorly to endothelial cells and protein-coated surfaces and exhibit defective spreading, aggregation, and chemotaxis. Patients with LAD 1 have recurrent bacterial and fungal infections involving skin, oral and genital mucosa, and respiratory and intestinal tracts; persistent leukocytosis (neutrophil counts of 15,000 to 20,000/μL) because cells do not marginate; and, in severe cases, a history of delayed separation of the umbilical stump. Infections, especially of the skin, may become necrotic with progressively enlarging borders, slow healing, and development of dysplastic scars. The most common bacteria are *Staphylococcus aureus* and enteric gram-negative bacteria. LAD 2 is caused by an abnormality of fucosylation of SLe^x(CD15s), the ligand on neutrophils that interacts with selectins on endothelial cells. It is now also known as *congenital disorder of glycosylation IIc* (CDGIIc).

DISORDERS OF NEUTROPHIL GRANULES The most common neutrophil defect is myeloperoxidase deficiency, a primary granule defect inherited as an autosomal recessive trait; the incidence is ~1 in 2000 persons. Isolated myeloperoxidase deficiency is not associated with clinically compromised defenses, presumably because other defense systems such as hydrogen peroxide generation are amplified. Microbicidal activity of neutrophils is delayed but not absent. Myeloperoxidase deficiency may make other acquired host defense defects more serious. An acquired form of myeloperoxidase deficiency occurs in myelomonocytic leukemia and acute myeloid leukemia.

Chédiak-Higashi syndrome (CHS) is a rare disease with autosomal recessive inheritance due to defects in the lysosomal transport protein LYST, encoded by the gene *CHS1* at 1q42. This protein is required for normal packaging and disbursement of granules. Neutrophils (and all cells containing lysosomes) from patients with CHS characteristically have large granules (Fig. 55-9). Patients with CHS have an increased number of infections resulting from many bacterial agents. CHS neutrophils and monocytes have impaired chemotaxis and abnormal rates of microbial killing due to slow rates of fusion of the lysosomal granules with phagosomes. NK cell function is also impaired.

TABLE 55-3 *Types of Granulocyte and Monocyte Disorders*

Function	Cause of Indicated Dysfunction		
	Drug-Induced	*Acquired*	*Inherited*
Adherence—aggregation	Aspirin, colchicine, alcohol, glucocorticoids, ibuprofen, piroxicam	Neonatal state, hemodialysis	Leukocyte adhesion deficiency types 1 and 2
Deformability		Leukemia, neonatal state, diabetes mellitus, immature neutrophils	
Chemotaxis—chemotaxis	Glucocorticoids (high dose), auranofin, colchicine (weak effect), phenylbutazone, naproxen, indomethacin, interleukin 2	Thermal injury, malignancy, malnutrition, periodontal disease, neonatal state, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, sepsis, influenza virus infection, herpes simplex virus infection, acrodermatitis enteropathica, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, hyper IgE–recurrent infection (Job's) syndrome (in some patients), Down syndrome, α-mannosidase deficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome
Microbicidal activity—oxygen	Colchicine, cyclophosphamide, glucocorticoids (high dose), TNF-α blocking antibodies	Leukemia, aplastic anemia, certain neutropenias, tuftsin deficiency, thermal injury, sepsis, neonatal state, diabetes mellitus, malnutrition, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, chronic granulomatous disease, defects in IFN-γ/IL-12 axis